A case for developing North-South partnerships for research in sickle cell disease

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For a better understanding of the pathophysiology and mechanisms of phenotypic diversity of sickle cell disease, and for the improvement of its management globally, there is a strong case for developing sustainable research partnerships between rich and poor countries. (Blood. 2005;105:921-923)

Introduction

The inherited disorders of hemoglobin, notably sickle cell (SS) disease and the thalassemias, are the most common monogenic diseases. As the result of intense selection due to heterozygote advantage against severe forms of malaria, they reach particularly high frequencies in many tropical countries and in any populations in which there are large immigrant populations from these regions. Many of the developing countries are passing through an epidemiologic transition in which, due to improved nutrition and control of infectious disease, childhood mortality rates are falling. Under these circumstances, the prevalence of genetic disorders like hemoglobinopathies tends to increase; affected children, who would previously have died in the first few years of life, are now surviving long enough to present for diagnosis and treatment. Hence, these diseases are presenting an increasingly serious global health problem.[1]

Although there have been improvements in the management of SS disease leading to longer survival in the developed countries, much remains to be learned about its pathophysiology and the mechanisms for its clinical diversity. Much less progress has been made in the developing countries in which the disease is common, where it is still an important cause of childhood mortality. We argue here that, both for furthering research and improving clinical care globally, there is a major case for developing long-term partnerships between research groups working on this disease in the rich and poor countries.

The extent of the problem

Based on heterozygote frequencies, SS disease occurs widely throughout sub-Saharan Africa, parts of the Middle East and, in a patchy distribution, the Indian subcontinent.[1-3] It also occurs in some European populations, notably Greece and Italy, and at a variable frequency in countries in which there have been major population movements from Africa: the United States, Brazil, and many countries of the Caribbean and Central America, for example. In many of these populations heterozygote rates range from 5% to 25% but, in certain regions (localized areas of Saudi Arabia, for example), up to 40% or more of the population may be carriers.

Very little is known about the overall health burden posed by SS disease. The World Health Organization has estimated that there may be approximately 216 000 babies born with SS disease in Africa each year and that the disease may account for 10% to 20% of neonatal mortality in West Africa.[4] However, in view of the rapidly changing epidemiology of infectious disease in Africa at the present time, these figures must be viewed with extreme caution. While projects such as the USA Cooperative Study of Sickle Cell Disease[5] and the Jamaican Cohort Study[6] have provided some indication of the patterns of survival and the major causes of death for particular age groups, very little data of this type are available for other populations. From such information that is published it appears that there is a wide range of morbidity and mortality at different ages, with a high death rate in childhood in many parts of Africa, ranging to an almost 100% survival to adult life in the Eastern Province of Saudi Arabia.[7,8]

One of the recurrent themes in clinical descriptions of sickle cell anemia in every population is the remarkable clinical diversity of the disease. This problem is highlighted by analyses of the financial burden of treating this condition in the United States; the bulk of hospitalizations are confined to a subset consisting of about 10% of the total patient population.[9] But, despite a great deal of work, with the exception of the coinheritance of α thalassemia or genetic determinants that produce relatively high levels of fetal hemoglobin,[10] very little progress has been made toward an understanding of the remarkable clinical diversity of this disease. In particular, virtually nothing is known about the relative roles of the environment and genetic factors in determining the clinical course.

There have been some genuine advances in the symptomatic management of SS disease. A reduction in mortality has been achieved in childhood by the use of prophylactic penicillin[11] and in adults by the administration of hydroxyurea,[12] and it has been established that the frequency of strokes can be reduced by transfusion.[13] Bone marrow transplantation has also shown limited success, although its role in this disease is not yet clearly defined.[14] However, the place for these approaches, and their potential cost, in the developing countries is not clear.

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The scientific case for international collaboration

As knowledge of the pathophysiology of SS disease has accumulated, it has become apparent that the basic genetic defect—that is, the increased capacity for hemoglobin S (Hb S) to polymerize—is only the tip of the iceberg of the widespread secondary pathology that is responsible for its complex phenotype. This includes an increased facility for sickle red cells to adhere to vascular endothelium, widespread rheologic and hemodynamic changes, endothelial damage and altered flow, platelet activation, abnormal cytokine response, and a variety of other changes.[15] Thus, although factors that modify the rate of polymerization of Hb S may be important, it is quite likely that many of the most serious complications of the disease result from either environmental or genetic factors that act "downstream" from the primary genetic defect.

Given this level of complexity, it is not surprising that it has been difficult to achieve an agreed classification of the different degrees of severity of SS disease. Regardless of the inevitable deficiencies of any classification of this kind, it is vital to attempt to produce a workable description of severity as a prelude to the potential international collaborations outlined here.

The central problem that needs addressing, and one that can only be achieved by international collaboration, is the relative roles of the environment and the genome in the clinical diversity of SS disease. Remarkably, there are still no twin or sibling-pair data that address this critical issue. Preliminary inquiries indicate that none of the rich countries have sufficient numbers of twin pairs to carry out a study of this type. Despite the well-known disadvantages of twin studies, they still offer the most direct approach to obtaining an approximate measure of the relative roles of nature and nurture in defining disease phenotypes and, while the role of the environment will vary between different regions, at least this approach will provide some badly needed information about its potential to modify the phenotype.

A more international approach to research in SS disease would also offer the opportunity for learning more about the genetic factors involved in phenotypic diversity. One of the most productive ways of searching for genetic modifiers in murine models of genetic disease is to examine phenotypic modification of single gene disorders bred into different genetic backgrounds and then to define the genes involved.[16] Sickle cell disease offers a unique opportunity for such studies in humans. As evidenced by β-globin–gene haplotype analysis, there is clear evidence for multiple origins of the Hb S gene. For example, the form of SS disease that occurs in parts of India and the eastern oasis populations of Saudi Arabia clearly has a different origin than that which predominates throughout the African subcontinent.[2,17] While the clinical differences in SS disease between these populations have been reasonably well documented,[7] they are by no means all explainable by the known genetic differences between them, notably the level of fetal hemoglobin and the frequency of α thalassemia. Indeed, even the reasons for the unusually high levels of Hb F production associated with the Arab-India haplotype have never been adequately explained. To what extent are some of these differences environmental or, if not, which other genes are involved? Similarly, other racial differences in the clinical features of SS disease have been observed but never explained.

Another important reason for evolving a more international approach to an understanding of the clinical diversity of SS disease relates to the evolutionary biology of the hemoglobinopathies. While it has been known for many years that the sickle cell gene has reached its high frequency by heterozygote protection against *Plasmodium falciparum* malaria,[18] it is only recently that case control studies have been applied to measure the degree of advantage in numeric terms. In at least some African countries, the sickle cell trait appears to confer approximately 80% resistance to the serious complications of malaria—that is, cerebral malaria and profound anemia.[19] Over recent years it has become apparent that relative resistance to malaria has had a remarkably broad effect on the genetic make-up of tropical populations, not only involving red cell polymorphisms but the HLA-DR system and a wide range of other proteins including inflammatory mediators, adhesion molecules, and agents like nitric oxide that are involved in vessel wall physiology.[20] Furthermore, and particularly as evidenced by the world distribution of the thalassemia mutations, the nature of these polymorphisms varies widely between different populations that have been exposed to malaria. This heterogeneous pattern of malaria-related polymorphism presumably reflects the action of particular mutations in different populations, intense selection and, most importantly, a relatively short exposure, at least in evolutionary terms, to the malarial parasite such that these protective mutations have not had time to become homogenized throughout the tropical world.[20]

If this interpretation of the heterogeneity of malaria-related genetic polymorphisms is correct, it follows that every population with a high frequency of the sickle cell gene will have a completely different genetic background of other malaria-related polymorphisms, many of which could have profound effects not just on propensity to different forms of infection but on a number of the other physiologic systems that are involved in the pathophysiology of the sickling disorders. Coselection of this type has been suggested recently as a basis for some of the clinical heterogeneity of the thalassemias[21]; exactly the same arguments are relevant to SS disease and its variants. Hence, this field offers a rich source for further study of candidate genes that might modify the phenotype of SS disease. Recent studies that have shown that the level of nitric oxide synthase has an important role in malaria susceptibility,[22] and the importance of nitric oxide in some of the vascular complications in sickle cell anemia,[23] offer an exciting example of these possibilities.

The clinical case for the mutual benefit of North-South interactions

The World Health Organization report *Genomics and World Health*[24] underlines the importance of transferring cost-effective DNA technology to the developing countries and cites the hemoglobin disorders as an important example of how this could be achieved, an argument that has been extended recently.[25] The development of a number of North-South research collaborations between sickle cell research groups in the rich countries and those in the developing world would, as a by-product, be of considerable benefit to the health and well-being of patients with SS disease in the developing world. In particular, interactions of this kind offer an opportunity to improve clinical and diagnostic facilities and hence the management of patients in the developing countries. For example, while it is clear that neonatal screening combined with prophylactic penicillin saves many lives in the richer countries, lack of knowledge of the causative organisms of deaths due to infection in infants in Africa and elsewhere casts uncertainty over the more general application of this approach. At the same time, the management of SS disease in the developed countries will undoubtedly be enhanced by a better understanding of the different

environmental and genetic factors that modify the phenotypes of the disease in their particular immigrant groups.

Considering the dire poverty and dysfunctional health care systems in many African countries, together with the huge mortality due to malaria, HIV/AIDS, and tuberculosis, it could be questioned as to whether this is the right time to encourage North-South partnerships for the study of a genetic disorder like SS disease. However, the different interactions between this condition and some of the major infectious killers in Africa may be of considerable practical importance. For example, knowledge of the high level of resistance of children with the sickle cell trait to severe malaria, combined with further information about the variability and magnitude of this protective effect in different countries, will be of considerable importance when designing vaccine trials for malaria, particularly if these entail attenuating rather than completely protective vaccines. Furthermore, the introduction of simple genetic technology as part of partnerships of this type provides a base of expertise for developing DNA diagnostics for other conditions, including the early diagnosis of infection and the identification of drug-resistant organisms or genetic factors that render individuals more or less likely to respond to anti-infectious agents.[24]

While these types of programs have evolved in the thalassemia field over many years,[26] this has not been the case for SS disease. As shown in the case of thalassemia, provided the research partnerships are sustainable for at least 5 to 10 years, they have the added effect of improving the clinical services in the poorer countries. Once a country has developed one or more centers of expertise based on these partnerships, it should then be possible for them to evolve local networks for helping countries in the same region to develop clinical and laboratory services at an improved level.[24] There is already preliminary evidence that it should be possible to develop similar programs for the study and management of SS disease in Africa.[27,28]

There are a number of requirements to be met before programs of this type can be instituted. First, scientists in the richer countries must be persuaded of their value and, through their parent institutions and funding agencies, must be given the opportunity to take a more global approach to SS disease. Second, these programs must be sustainable over a reasonably long period. Finally, they have to be combined with local public health and educational developments in the developing countries. These issues, particularly funding, have been discussed in more detail recently.[24,25,29] It is particularly important that clinical investigators in this field enter into a dialogue with national and international funding bodies to encourage the development of these potentially cost-effective partnerships, which would be of mutual benefit to both developed and developing countries.

Summary

The case for developing scientific partnerships between rich and poor countries to tackle the problems of the natural history and mechanisms for clinical diversity of Hb S disease and related disorders is extremely strong. Building international links of this kind also offers an opportunity to improve clinical services for this distressing disease in the developing world and for minority communities in developed nations. For these reasons, serious consideration should be given to the establishment of partnerships between research centers in the richer countries and those in Africa, the Middle East, and India.

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